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CHEMISTRY & BIOCHEMISTRY OF SULFA DRUGS: THE INHIBITOR OF DIHYDROPTEROATE SYNTHESIS *IN-VIVO*

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ABSTRACT

Sulfonamide is a frictional group that is the basis of several groups of drugs, which are called sulphonamides, salfa drugs or sulpha drugs. The original antibacterial sulfonamides are synthetic antimicrobial agents that contain the sulphonamide group. Sulfonamide formulations are supplied as combination of products having two main components, a sulfonamide and the synthetic diaminopyrimidines, trimethoprim and ormethoprim. These combinations are made that it acts on specific targets in bacterial DNA synthesis. Sulfonamides inhibit the bacterial enzyme dihydropteroate synthesis in the folic acid pathway. Sulfonamide antibiotics are used as veterinary medicines to treat infections in livestock herds. Moreover, sulfonamides are widely used such as anticancer, anti-inflammatory and antiviral activity. Allergies to Sulfonamids are common. The overall incidence of adverse drug reactions to sulfa antibiotics is approximately 3%, close to penicillin, hence medications containing sulfonamides are prescribed carefully. Highest tissue concentrations of sulfonamide plus metabolites are found in the liver and kidney of various food-producing species, but the rather high rate of sulfonamide related violations in pig liver has decreased considerably over the past decades.

KEYWORDS: Diaminopyrimidines, Trimethoprim, Ormethoprim, Dihydropteroate, Anticancer, Antiinflammatory, Antiviral.

INTRODUCTION

The term sulphonamides are employed as a generic name for the derivatives of para-amino benzene sulphonamide (sulphanilamide). The sulphonamide drugs were the first effective chemotherapeutic agents to be employed systemically for the prevention and treatment of bacterial infections in humans. The sulphonamides are bacteriostatic antibiotics with a wide spectrum action against most gram-positive bacteria and many gram-negative organisms. Actually, it was found to be the metabolic product of Prontosil, which is responsible for antibacterial activity, and this has given the initiation to develop sulphonamides as antibacterial agents.[1-3]

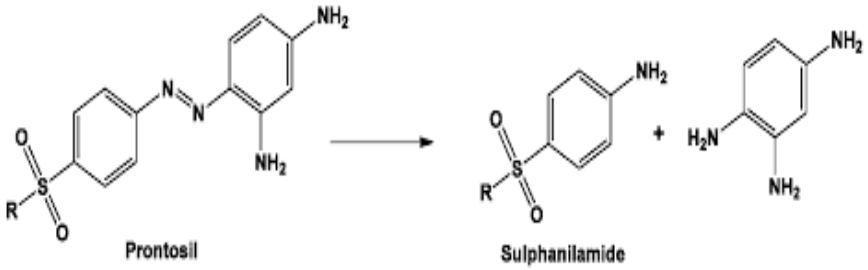


Figure-1: *In-vivo* metabolism of prontosil.

Sulphonamides are total synthetic substances that are produced by relatively simple chemical synthesis. The advent of penicillin and, subsequently of other antibiotics has diminished the usefulness of sulphonamides. Antimicrobial compounds contain sulphonamide (SO_2NH_2) group. This group (SO_2NH_2) is also present in other compounds, such as antidiabetic agents (e.g. Tolubutamide), diuretics (e.g. chlorthiazide and its congeners, furosemide, and acetazolamide), and anticonvulsants such as sulthiame. The sulphonamides exist as white powder, mildly acidic in character, and they form water-soluble salts with bases. The pH of sodium salts with some exception, for example, sodium sulphacetamide, is very high when given intramuscular

(IM), the marked alkalinity causes damage to the tissues. Microorganisms that may be susceptible in vitro to sulphonamides include *Streptococcus pyogens, Streptococcus pneumoniae, Haemophilus influenzae, H. ducreyi, Nocardia, Actinomyces, Calymmatobacterium granulomatis, and Chlamydia trachomatis*. The minimal inhibitory concentration ranges from 0.1 μg/ml for *C. trachomatis* to 4–64 μg/ml for *E. coli*. Sulphonamides are selective drugs used to treat urinary tract infections, bacterial respiratory infections, and gastrointestinal (GI) infections.[4-6]

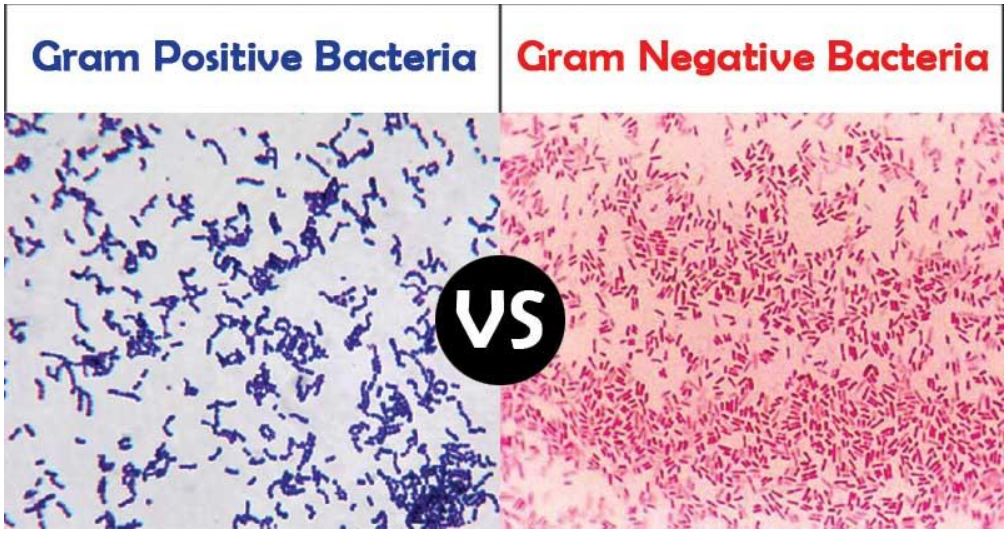


Figure-2: Gram-positive & Gram-negative bacteria.

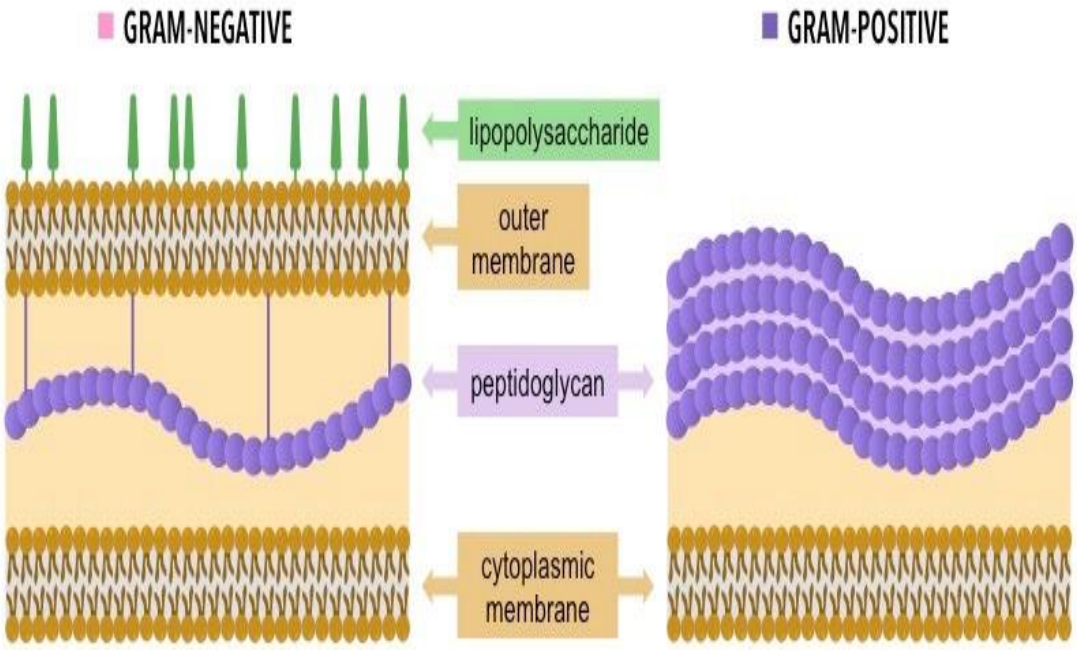


Figure-3: Difference between cell wall design of Gram+ve & Gram-ve bacteria.

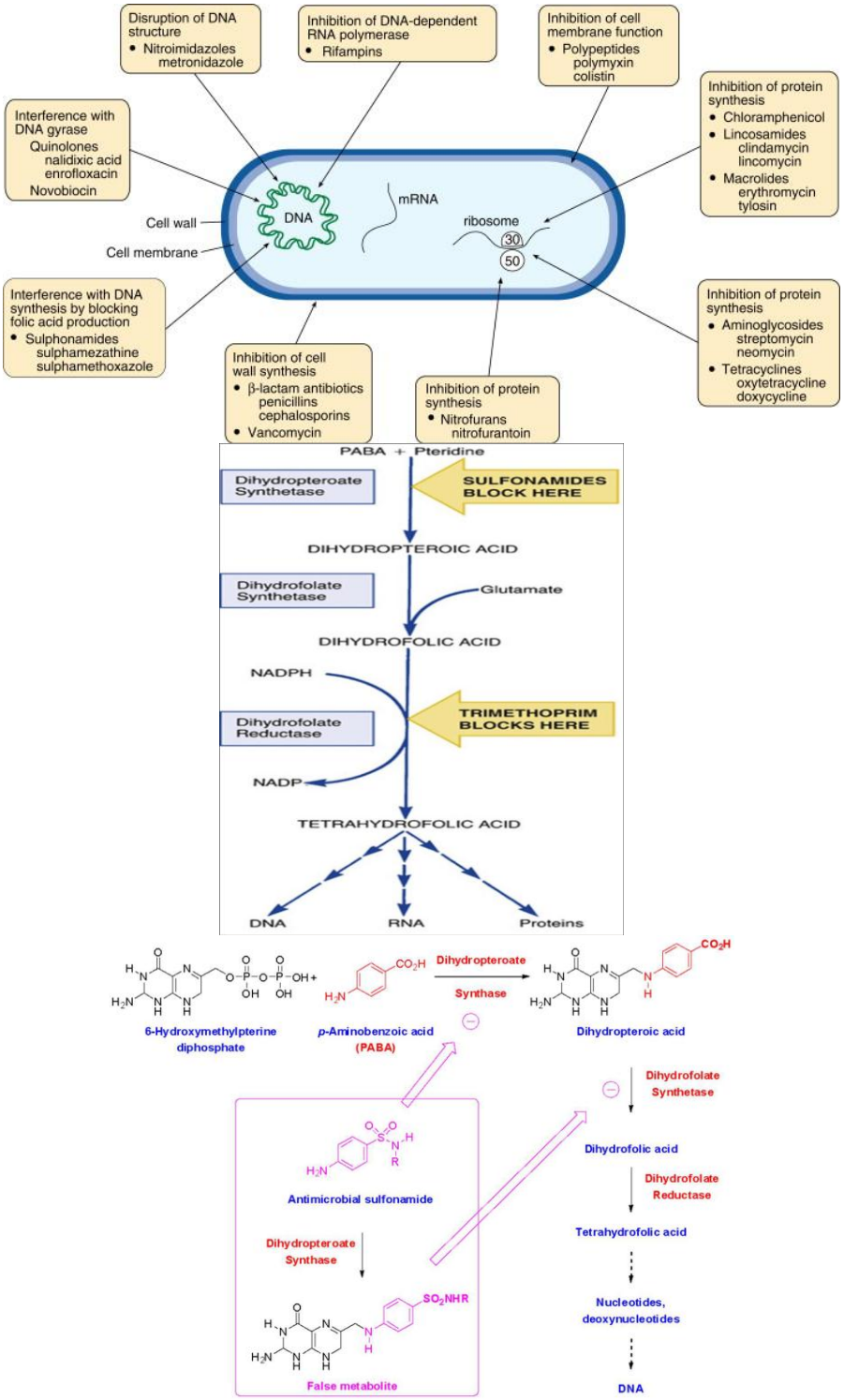


Figure-4: Mechanism of action of Sulphonamide.

SAR OF SULPHONAMIDES

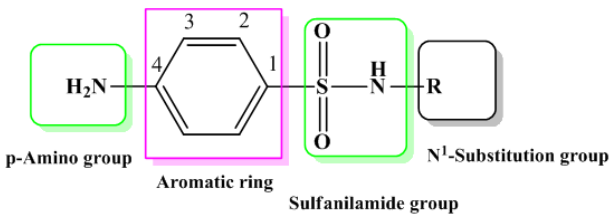


Figure-5: Chromophore of sulphonamide moiety.

➢ Sulphanilamide skeleton is the minimum requirement for antibacterial activity.
➢ Sulphur atom should be directly linked to benzene ring.
➢ Replacement of the benzene ring by other ring system decreases the activity.
➢ Replacement of SO_2NH group by -CONH reduces the activity.
➢ The sulphonamide nitrogen must be primary or secondary.
➢ The aromatic ring and the sulphonamide functional group are both required and both must be directly attached to the aromatic ring.
➢ The aromatic ring must be para – substituted only.[7-9]

PHARMACOKINETICS

- A - Rapidly and well absorbed orally
- D - Widely distributed in the body
  - Crosses BBB and placenta
  - Accumulates in prostatic fluid
  - Extent of plasma protein binding differs → Longer acting agents are highly protein bound
- M - Acetylation in the Liver → acetylated metabolites are inactive but still contribute to S/E Less soluble in ACIDIC URINE → Precipitation of

CRYSTALLURIA → RENAL TOXICITY

- E - Kidney by glomerular filtration

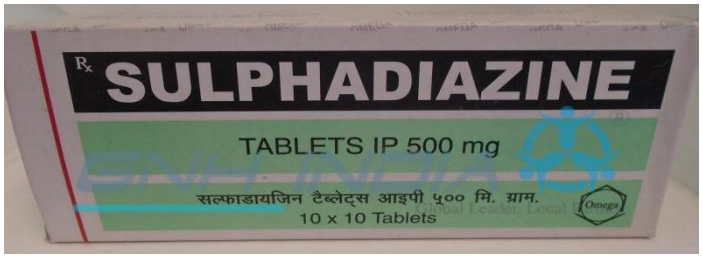
* More lipid soluble agents are highly reabsorbed → longer acting

CLASSIFICATION ACCORDING TO DURATION OF ACTION

❖ **Orally absorbable agents**

- **Short acting (6-9hrs)** -

➢ Sulfadiazine
➢ Sulfacytine
➢ Sulfamethizole
➢ Sulfisoxazole



❖ **Intermediate acting (10-12 hrs)**

➢ Sulfamethaxazole
➢ Sulfamoxole

- Long acting (7days)

➢ Sulfadoxine
➢ Sulfamethopyrazine

❖ Orally non absorbable agents

➢ Sulfasalazine
➢ Olsalazine

❖ Topical agents

➢ Silver sulfadiazine Sulfacetamide Mafenide

CLASSIFICATION ACCORDING TO THERAPEUTIC USE

Topically applied sulfonamides

For eye infection-

➢ Sulfacetamide(10%,20%&30%)

For skin infection-

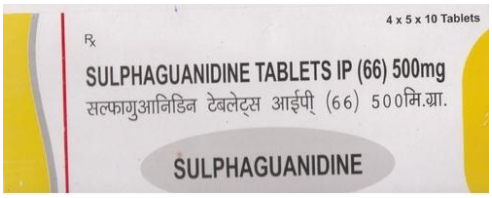
➢ Silver sulfadiazine
➢ Mefanide acetate

GIT Infections

➢ Succinyl sulfathaizole,
➢ Phthalyl sulfathiazole,
➢ Sulfaguanidine

Meningitis

➢ Sulfadiazine,
➢ Sulfadimidine



UTI Infections
- Sulfisoxazole,
- Sulfamethopyrazine

Respiratory tract infections
- Sulfaphenazine,
- Cotrimoxazole

Leprosy
- Dapsone,
- Solapsone

Drugs for bowel disinfection
- Sulfasalazine,
- Pthalylsulfathiazole

Malaria
- Sulfadoxine + Pyrimethamine

Nocardiosis
- Sulfadiazine,
- Sulfisoxazole

GENERAL SYNTHESIS OF SULFONAMIDES

The most common method of sulfonamide synthesis involves a reaction of corresponding aliphatic or aromatic sulfonyl chloride with ammonia or an adequate amine. This synthesis method represents the simplest and direct pathway to obtain sulfonamides, wherein the sulfonamide yield is high. This will be explained in detail in the case of sulfanilamide.

The initial compound for a multistep sulfanilamide synthesis is nitrobenzene. Nitrobenzene can be reduced using tin, as a reducing agent, and hydrochloric acid to give the anilinium ion, which can be converted to aniline using sodium hydroxide. Acetanilide, a compound insoluble in water, can be derived from aniline by the reaction of acetylation in the aqueous medium. The next step in the synthesis is the reaction of the electrophilic aromatic substitution in which acetanilide reacts with chlorosulfonic acid to give the intermediate 4-acetamidobenzenesulfonyl chloride. The formed intermediate, in the presence of ammonia, gives 4-acetamidobenzene sulfonamide. The acetamide group causes the substitution almost completely in the para position. In the final step of the synthesis, the protecting acetamide group undergoes to hydrolysis in acidic medium and forms 4-aminobenzenesulfonamide, sulfanilamide. The synthesis of sulfanilamide is presented in figure below.[10-12]

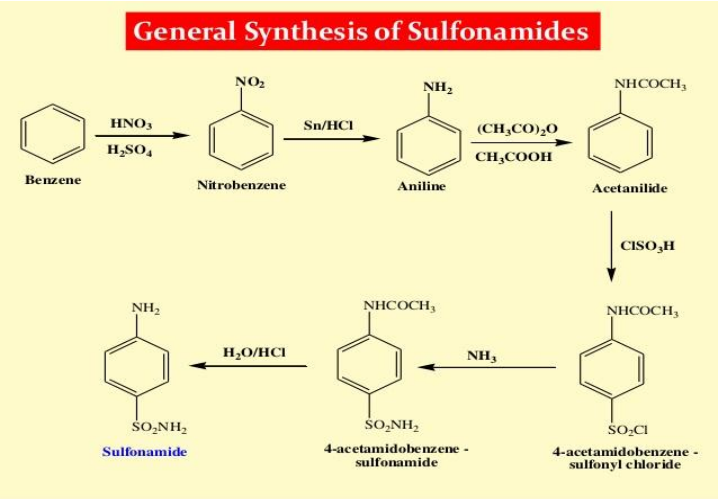


Figure-6: Scheme of synthesis.

ANTIMICROBIAL ACTIVITY: Sulfonamides are antimicrobial drugs with a broad spectrum of action, effective against Gram-positive and certain Gram-negative bacteria, such as intestinal bacteria *Escherichia coli, Klebsiella, Salmonella, Shigella and Enterobacter* species. Sulfonamides show a good activity against *E. coli*, moderate against *Proteus mirabilis* and *Enterobacter* species and weak against *Klebsiella*, but they show no inhibitory activity against *Pseudomonas aeruginosa* and *Serratia* species. They are effective

against species of *Chlamydia* genus. Sulfonamides are also effective against fungi (*Pneumocystis carinii*) and protozoa (*Toxoplasma gondii*). Sulfonamides differ in potency, but not in the spectrum of the antimicrobial activity.[13-15]

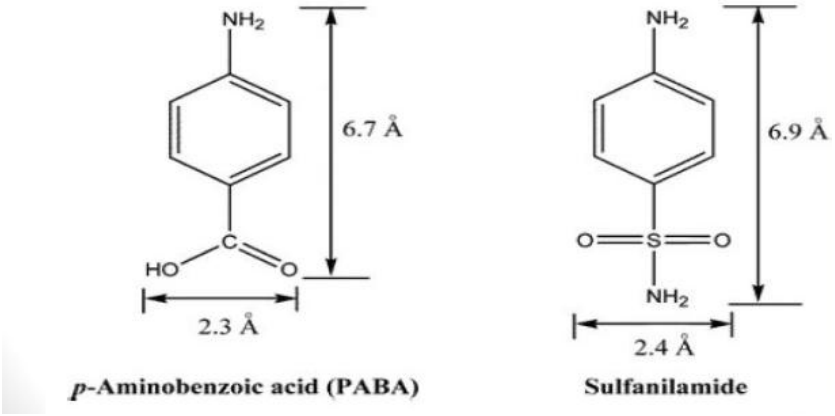


Figure-7: Structural similarity between PABA & Sulphonamide.

ANTIBACTERIAL SPECTRUM[16-18]

Sensitive Organisms

- *S. pyogenes*
- *H. influenza*
- *H. ducreyi*
- *C. granulomatis*
- *Chlamydiae species*
- *Actinomyces*
- *Nocardia*
- *Toxoplasma*

- Mechanism of Resistance
  - Due to mutations causing:

a) Overproduction of PABA
b) Altered nature of dihydropteroic acid synthetase
c) Loss of permeability of sulfonamides through bacterial membrane
d) Appearance of an alternative pathway

- Resistant Organisms
  - *Gonococci*
  - *Staphylococci*
  - *Meningococci*
  - *Streptococci*
  - *E. coli*
  - *Shigella*

CLINICAL USES

A. Orally Absorbable Drugs
- Acute uncomplicated UTI
- Third Choice Drug

- Nocardiosis
- Chancroid (*H. ducreyi*)
- Lymphogranuloma (Chlamydia)

B. Oral Non-Absorbable Drugs
- Sulfasalazine is the Drug of choice for ulcerative colitis
- Sulfasalazine is also used in Rheumatoid Arthritis

C. Topical Agents
- Sodium Sulfacetamide → Ophthalmic solution / ointment

- Trachoma - Chlamydia trachomatis
- Bacterial Conjunctivitis

- Silver sulfadiazine → Least toxic, preferred over mafenide

- Prophylaxis / infections in Burns
- Active against *Pseudomonas*

ADVERSE EFFECTS

1. **Crystalluria + Renal toxicity**

- Dose Related

Risk can be minimized by taking plenty of fluids and Alkalinizing Urine

Acetylated metabolites are less soluble in acidic urine

↓

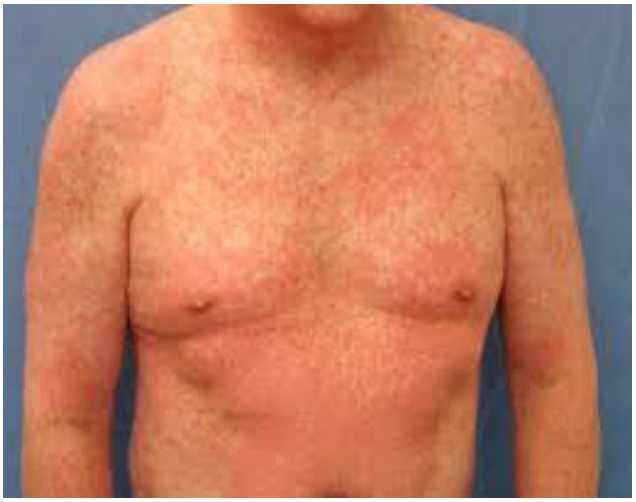
Precipitates in kidney and renal tubules

↓

Causes crystalluria and renal obstruction

2. **Hypersensitivity Reactions**

- Rashes-especially at mucocutaneous Junctions



- Steven's johnson's syndrome-erythema multiforme, ulcerations of mucous membranes, malaise
- Eosinophelia
- Drug Fever
- Exfoliative dermatitis

3. **Haemolysis**

- Can occur in patients with G6PD deficiency
- Neutropenia. Agranulocytosis and thrombocytopenia can occur

4. **Kernicterus in Neonates**

- Can be precipitated especially in **premature infants** since their blood brain barrier is not fully developed.

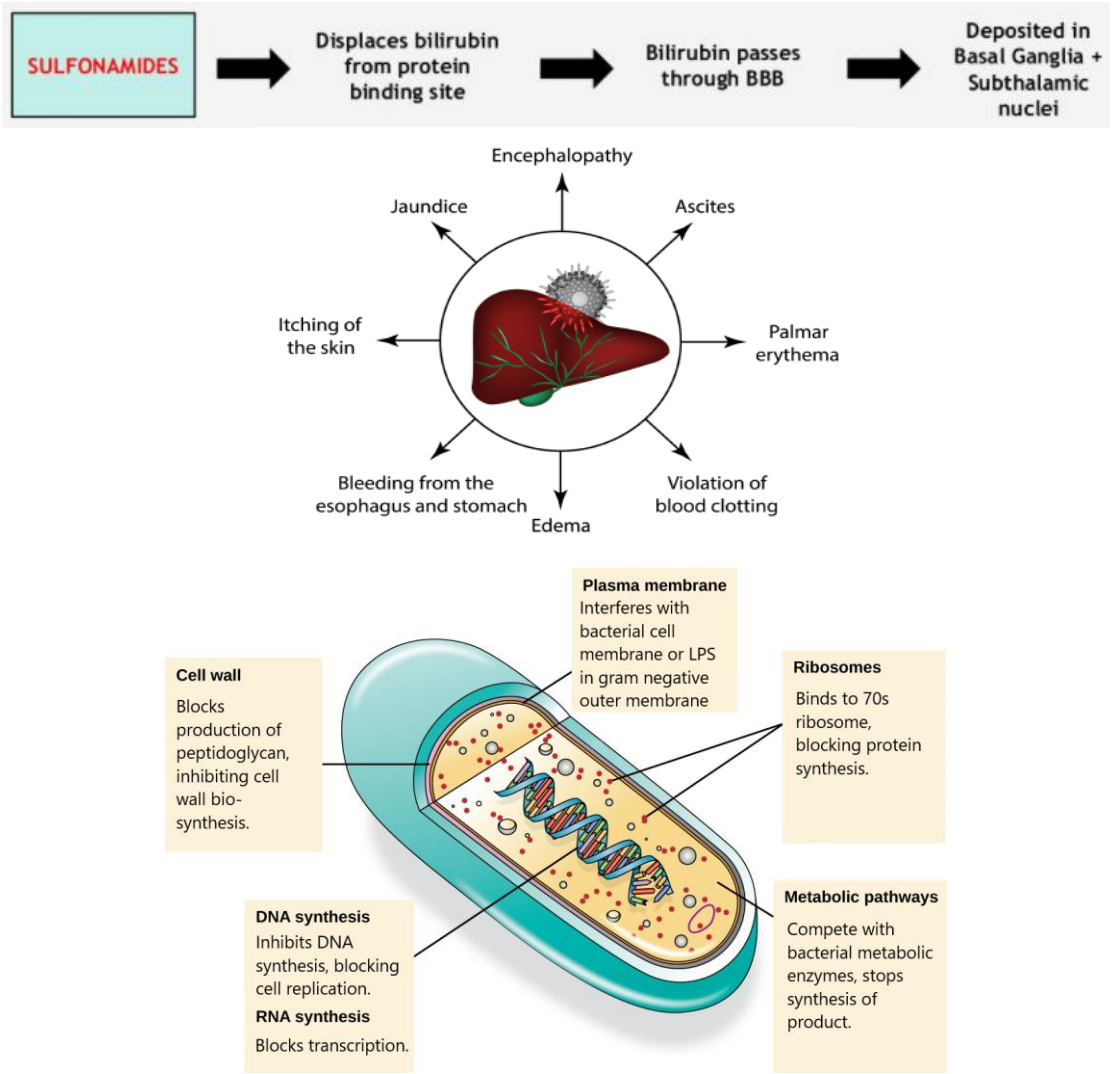


Figure-8: Bacterial cell anatomy.

5. **Nausea, Vomiting, Epigastric Pain**
6. **Hepatitis**

CONCLUSION

Sulfonamide antimicrobial drugs represent an important class of synthetic substances with different physicochemical, pharmacokinetic, and pharmacodynamic characteristics. Sulfonamides are used in the therapy of urogenital, gastrointestinal, and respiratory tract infections, then for the eye, skin and mucous membrane infections, as well as in the prevention and treatment of burn infections. The sulfonamides application in the therapy is partially limited by the bacterial resistance and sulfonamides side effects. In order to overcome the resistance and to reduce the adverse effects, continuous efforts are made to synthesize novel antimicrobial compounds with the sulfonamide structure and to develop novel formulations with the existing sulfonamide substances. On the other side, the sulfonamides application in therapy leads to their introduction into the environment and maintaining the resistance. The environment fate of sulfonamides depends on the influence of various biotic and abiotic factors such as the presence of some degrading bacteria and fungi, temperature, pH, and UV radiation. Additionally, numerous techniques can be applied in order to degrade and remove present sulfonamides from different compartments of the environment. Sulfonamide's degradation leads to the formation of less active and toxic compounds, and in the end, carbon dioxide and water. In that way, the sulfonamides presence in the environment can be limited.

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